PATENT
Docket No.: **176/60197 (6-11405-675/676)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Rosenblatt et al.	Examiner: Larry R. Helms
Serial No.	:	09/016,743	Art Unit: 1642
Cnfrm. No.	:	7389	
Filed	:	January 30, 1998	
For	:	CHIMERIC ANTIBODY FUSION PROTEINS FOR THE RECRUITMENT AND STIMULATION OF AN ANTITUMOR IMMUNE RESPONSE	

APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

Pursuant to 37 CFR § 1.192, appellants hereby file their appeal brief in triplicate. Enclosed is the filing fee of $165.00 required by 37 CFR § 1.17(c). The Commissioner is hereby authorized to charge/credit Deposit Account No. 14-1138 for any deficiency/overage.

I. REAL PARTIES IN INTEREST

The University of Rochester and the Regents of the University of California, as assignees of U.S. Patent Application Serial No. 09/016,743, are the real parties in interest.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences pertaining to the above-identified application.

III. STATUS OF CLAIMS

A. Claims 1, 3-10, and 25 Are Rejected

Claims 1, 3-8, 10, and 25 have been rejected under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 5,824,782 to Hölzer ("Hölzer") in view of Huston et al., "Protein Engineering of Single-Chain Fv Analogs and Fusion Proteins," Methods Enzymology, 203:46-88 (1991) ("Huston"). Claims 1 and 9 have been rejected under 35 U.S.C. § 103(a) for obviousness over Huston in view of U.S. Patent No. 5,514,554 to Bacus ("Bacus") and Hölzer. Claims 1, 3-10, and 25 have been rejected under U.S.C. § 112 (2nd para.) for indefiniteness. Claims 1, 3-10, and 25 have been rejected under U.S.C. § 112 (1st para.) for lack of descriptive support.

B. Claims 2, 11-24, and 26-76 Have Been Canceled

Claims 2, 11-24, and 26-76 have been canceled.

C. No Claims are Allowed

No claims are allowed.

D. Claims 1, 3-10, and 25 Are On Appeal

The decision of the examiner rejecting claims 1, 3-10, and 25 is appealed. These claims, in their currently pending form, are set forth in the attached Appendix.

IV. STATUS OF AMENDMENTS

Concurrent with the filing of this appeal brief, appellant has filed its Amendment Under 37 C.F.R. §1.116 to respond to the Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures, which was attached to the outstanding office action. This amendment amends the specification in order to comport with the requirements of 37 C.F.R. §§ 1.821-1.825 and amends FIG. 2 to correct a typographical error.

V. SUMMARY OF INVENTION

A. Problems In The Prior Art

The management of residual disease is a central problem in breast and other solid tumors (page 1, lines 27-28 of U.S. Patent Application Serial No. 09/016,743). Despite efforts to maximize dose intensity, relapse remains a critical and generally fatal problem in high risk breast cancer patients (page 1, lines 28-30). Chemotherapeutic strategies are necessarily limited by various toxicities, and of limited efficacy against nonproliferating tumor cells (page 1, lines 31-33). Additional modalities, which will achieve further cytoreduction are needed (page 1, lines 33-34). A variety of investigators have suggested the use of gene transfer techniques to augment immunogenicity of cancer cells, and provoke an immune tumor-directed response (page 1, lines 34-37). Many of these strategies involve *ex vivo* manipulation of tumor cells, are technically difficult to implement, and do not target systemic tumor deposits (page 1, line 37 – page 2, line 2).

Although various different trials of monoclonal antibodies, antibody based conjugates and/or radioantibody have been performed, with limited success, results of these trials have highlighted obstacles to successful antibody therapy of human malignancy (page 2, lines 3-7). Antibody opsonization generally does not result in direct cytotoxicity, due to poor fixation of complement and/or poor enlistment of antibody dependent cytotoxicity (ADCC) (page 2, lines 7-16). Strategies based on direct antibody-based killing (e.g. antibody-toxin conjugates such as antibody-ricin, or radiolabelled antibody strategies, e.g. ^{131}I-Ab) require delivery to all tumor cells and are hampered by limited vascular permeability to proteins of 150kd or greater (mw of IgG) and extravascular diffusion ability (page 2, lines 16-29). Elevated interstitial pressures within tumor masses due to absent/poorly organized lymphatics further impede delivery (page 2, lines 29-31). Antibody (Ab) and cytokine activation of effector cells may be more effective than Ab alone (page 2, line 31 – page 3, line 2).

Stimulation of an antitumor immune response is a stepwise process requiring the accumulation and activation of immune effector cells in the vicinity of tumor cells (page 3, lines 3-5). Monocytes and lymphocytes initially interact with adhesion molecules on endothelial cells, followed by migration of immune effector cells in response to chemotactic gradients in tissues (page 3, lines 6-9). Effector cells in the tumor vicinity are then available for activation and subsequent stimulation of an antitumor immune response (page 3, lines 9-

11). Chemokines are low molecular weight proteins that act as potent chemoattractants, and are involved in migration of inflammatory cells (page 3, lines 11-13). They are divided according to the configuration of the first cysteine residues at the amino terminus of the protein (page 3, lines 13-15). Different subfamilies of chemokines have been shown to attract different classes of inflammatory cells (page 3, lines 15-17). C-C chemokines predominantly attract monocytes and lymphocytes, while C-X-C chemokines attract neutrophils in addition to lymphocytes (page 3, lines 17-21). RANTES is a member of the C-C chemokine family and is a potent chemoattractant of T cells, NK cells, monocytes, eosinophils, basophils and dendritic cells (page 3, lines 21-28). RANTES, present at high concentrations (1 μM), has also been shown to stimulate T cell activation and proliferation (page 3, lines 28-35). RANTES-mediated T cell activation can also lead to the generation of an antitumor immune response and tumor rejection as shown in gene transfer studies performed in murine syngeneic *in vivo* EL4 lymphoma and MCA-205 tumor models (page 3, line 35 – page 4, line 9). Therefore, direct delivery of RANTES to tumor deposits may assist in recruitment and/or the molecule may be used as a modulator for cancer immunotherapy (page 4, lines 9-11).

T-cell activation and proliferation requires two signals from antigen-presenting cells (APCs) (page 4, lines 12-13). The first signal is antigen specific and mediated by recognition of antigenic peptides presented in the context of MHC-I or II by the T-cell receptor (TCR) (page 4, lines 13-16). A second or "costimulatory" signal can be provided *via* binding of a costimulatory ligand of the B7 family on the APC to the CD28 counterreceptor present on T-cells (page 4, lines 16-19). The B7 family includes several Ig-like molecules including B7.1 and B7.2 (page 4, lines 19-20). Provision of signal 1 without signal 2 may lead to a state of immune tolerance (page 4, lines 20-24). B7.1 gene transfer into nonimmunogenic tumor cells has been shown to elicit a T-cell-mediated immune response not only against transfected (B7+) but also against parental nontransfected tumor cells (page 4, line 24 – page 5, line 15). Since T-cell activation requires both B7.1 activation and TCR engagement, only cells with TCRs which recognize antigenic determinants on tumor cells should be activated (page 5, lines 16-25).

Chemical conjugation of antibody to cytokines instead of fusion has resulted in decreased T-cell activation by the conjugate although effects on vascular permeability are preserved (page 5, lines 26-33). In contrast, recent studies using an anti-tumor antibody-IL-2

fusion protein suggest retention of both antibody specificity and cytokine function in the fusion molecule (page 5, line 33 – page 6, line 25).

B7.1 gene transfer is not always a realistic option for treating cancer in a mammal (page 6, lines 26-27). B7.1 gene transfer requires either *ex vivo* manipulation of tumor cells which is technically difficult, or *in vivo* delivery *via* gene therapy vectors which would not specifically target systemic tumor deposits (page 6, lines 27-31). An effective method would not rely on absolute kill of all tumor cells by antibody/conjugate nor upon delivery to all tumor cells to elicit a response (page 6, lines 31-33). The present invention overcomes the significant problems with biodistribution and delivery associated with prior methods (page 6, lines 33-35).

B. Brief Description Of The Invention

The present invention relates to a chimeric molecule having a binding domain capable of binding to a tumor cell associated antigen and a chemokine or an active fragment of a chemokine (page 7, lines 3-6 of U.S. Patent Application Serial No. 09/016,743). The chimeric molecule is connected such that the binding domain remains capable of binding to the tumor cell associated antigen and the chemokine or fragment of the chemokine retains its activity (page 7, lines 6-9).

The present invention provides a novel approach for the stimulation of an anti-tumor immune response using chimeric molecules to facilitate immune eradication of breast, ovarian and other cancer cells (page 14, lines 8-11). In particular, the present invention provides chimeric molecules directed against known tumor associated antigens, e.g., Her2/neu and CEA, connected to the chemokine RANTES, or to the extracellular domain of the T-cell costimulatory ligand B7.1 (page 14, lines 11-16).

VI. ISSUES

A. Whether claims 1, 3-8, 10, and 25 are properly rejected under 35 U.S.C. § 103(a) for obviousness over Hölzer in view of Huston, in view of the evidence of record that those skilled in the art would not have adapted Huston's single-chain Fv analog technology to immunoconjugates like those of Hölzer.

B. Whether claims 1 and 9 are properly rejected under 35 U.S.C. § 103(a) for obviousness over Huston in view of Bacus and Hölzer, where Bacus does not overcome the above-noted deficiencies of Hölzer and Huston.

C. Whether claims 1, 3-10, and 25 are properly rejected under 35 U.S.C. § 112 (2nd para.) for indefiniteness, where those skilled in the art would understand what is meant by a complete antibody and how it binds in accordance with the present invention.

D. Whether claims 1, 3-10, and 25 are properly rejected under 35 U.S.C. § 112 (1st para.) for lack of descriptive support, where the present application clearly teaches the use of complete antibodies.

VII. GROUPING OF CLAIMS

Dependent claims 3-10 and 25 stand or fall with the independent claim from which they depend.

VIII. ARGUMENTS

A. Applicable Law

1. 35 U.S.C. § 103

35 U.S.C. § 103 imposes the requirement that an invention, to be patentable, must not have been obvious over the prior art "at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." The starting point for discussion of obviousness is Graham v. John Deere Co., 383 U.S. 1 (1966), which set forth the following factors for determining obviousness: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) such objective evidence of non-obviousness as commercial success, long felt-but unresolved needs, and failure of others. All evidence must be weighed before reaching a conclusion on obviousness under § 103. Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1561, 1 USPQ2d 1593, 1594 (Fed. Cir.), cert. denied, 481 U.S. 1052 (1987); Hodosh v. Block Drug, 786 F.2d 1136, 1143, 229 USPQ 182, 188 (Fed. Cir.), cert. denied, 479 U.S. 827 (1986); Simmons Fastener Corp. v. Illinois Tool Works, 739 F.2d 1573, 1575, 222 USPQ 744, 746 (Fed. Cir. 1984), cert. denied, 471 U.S. 1065 (1985). In addition, the prior art itself must suggest the desirability and, therefore, obviousness of a modification of a reference or the combination of references to achieve a claimed invention. Hodosh v. Block

Drug, 786 F.2d at 1143 n.5, 229 USPQ at 187 n.5; In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

2. 35 U.S.C. § 112

The "written description" requirement under 35 U.S.C. § 112 (1st para.) has been held to be distinct of the "enablement" requirement of this same section. See Vas-Cath v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The purpose of the "written description" requirement is to ensure that the inventor had possession of the invention claimed at the time the application was filed. Id. To achieve this, the application must in some manner describe the invention with all its claimed limitations. See Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1979).

Finally, 35 U.S.C. § 112 (2nd para.) requires that the claims of an application "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." In determining whether claim language is sufficiently definite, a determination is made whether "one skilled in the art would understand the bounds of the claim when read in light of the specification." Allen Eng'g Corp. v. Bartell Indus. Inc., 299 F.3d 1336, 1348, 63 USPQ2d 1769, 1775 (Fed. Cir. 2002) (citing Personalized Media Communs., LLC v. ITC, 161 F.3d 696, 705, 48 USPQ2d 1880, 1888 (Fed. Cir. 1998)).

B. The Rejection of Claims 1, 3-8, 10, and 25 Under 35 U.S.C. § 103(a) for Obviousness Over Hölzer in View of Huston Is Improper

1. Description of Hölzer

Hölzer discloses immunoconjugates which comprise a monoclonal antibody or fragment thereof, which is specific for the human EGF-receptor molecule, and a member of the chemokine family. The member of the chemokine family is preferably selected from C-X-C family, such as Interleukin-8 (IL-8). The immunoconjugates induce cytotoxic and chemotactic activity and are suitable for a targeted tumor therapy. Hölzer's immunoconjugate binds the N-terminus of IL-8 to the carboxy terminus of the Fab fragment of the monoclonal antibody.

2. Description of Huston

Huston relates to the protein engineering of single-chain Fv analogs and fusion proteins. In these constructs, the single-chain Fv analogs are variable region fragments of antibodies which consist of a heavy-chain variable region domain V_H non-covalently associated with a light-chain variable domain V_L in the form of a single chain. This single-chain Fv analog is prepared by connecting the genes encoding the V_H domain and the V_L domain with an oligonucleotide and recombinantly producing the V_H and V_L domains with a linker peptide between them (page 47). The single-chain Fv consists of a single polypeptide chain with the sequence V_H-linker-V_L or V_L-linker-V_H, as opposed to the classical Fv heterodimer of V_H and V_L (page 51). Native IgG antibodies not only contain V_H and V_L domains, but also constant region C_H1, C_H2, and C_H3, with all of these components arranged with respect to one another in a particular fashion (page 49). The single-chain Fv analogs not only lack the constant regions of native IgG, but also the native conformation of such antibodies (page 49).

3. The Combination of Hölzer and Huston Would Not Have Rendered the Claimed Invention Obvious

It is the examiner's position that the chimeric molecule comprising a chemokine coupled to the N-terminus of the heavy or light chain of a complete antibody, as disclosed in the present invention, would have been obvious in view of the combination of Hölzer and Huston. Hölzer is cited as teaching antibodies with chemokines at the C terminus. Huston is cited as teaching conjugation at the N terminus.

A proper *prima facie* showing of obviousness requires the examiner to satisfy three requirements. First, the prior art relied upon, coupled with knowledge generally available to one of ordinary skill in the art, must contain some suggestion which would have motivated the skilled artisan to combine references. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the examiner must show that, at the time the invention was made, the proposed modification had a reasonable expectation of success. See Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Finally, the combination of references must teach or suggest each and every limitation of the claimed invention. See In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Appellants submit that Hölzer and Huston do not establish a *prima facie* case of obviousness pursuant to these requirements.

Hölzer's immunoconjugate binds the N-terminus of IL-8 to the carboxy terminus of the Fab fragment of the monoclonal antibody. Thus, Hölzer does not satisfy the requirement of the claimed invention that the chemokine be "coupled to the N-terminus of the heavy or light chain of the antibody".

The portion of Huston relied on in the examiner's rejection relates to the protein engineering of single-chain Fv analogs and fusion proteins. In these constructs, the single-chain Fv analogs are variable region fragments of antibodies which consist of a heavy-chain variable region domain V_H non-covalently associated with a light-chain variable domain V_L in the form of a single chain. As explained on page 47, this single-chain Fv analog is prepared by connecting the genes encoding the V_H domain and the V_L domain with an oligonucleotide and recombinantly producing the V_H and V_L domains with a linker peptide between them. Thus, as noted in the following passage on page 51, the single-chain Fv analog of Huston is distinguishable from the claimed complete antibody:

> The single-chain Fv consists of a single polypeptide chain with the sequence V_H-linker-V_L or V_L-linker-V_H, as opposed to the classical Fv heterodimer of V_H and V_L.

Moreover, native IgG antibodies not only contain V_H and V_L domains but also constant regions C_H1, C_H2, and C_H3, with all of these components arranged with respect to one another in the particular fashion shown in Figure 1A on page 49 of Huston. The single-chain Fv analogs of Huston not only lack the constant regions of IgG but also the native conformation of such antibodies. Since Huston does not utilize complete antibodies, it is clearly distinguishable from the claimed invention.

As demonstrated in the Declaration of Seung-Uon Shin Under 37 C.F.R. § 1.132 ("Shin Declaration"), submitted with Preliminary Amendment dated July 19, 2002, one of ordinary skill in the art would have no basis to adapt the teachings of Huston regarding single-chain Fv analogs to the whole antibody immunoconjugates of Hölzer. In particular, scientists skilled in the field of antibody-based cancer therapeutics would not regard information relating to immunoconjugates of single chain Fv analogs as relevant to immunoconjugates made from whole antibodies (Shin Declaration ¶ 4). As explained below,

there are significant differences with regard to the avidity, half life, and chemokine carriage which would cause scientists skilled in the field of antibody cancer therapeutics to avoid adapting single chain Fv analog technology to whole antibody cancer therapeutics (Id.).

With regard to avidity, whole antibodies have two binding sites, while single chain Fv analogs have one binding site (Shin Declaration ¶ 5). Although they have exactly the same affinities, whole antibodies show higher binding ability to antigen than single chain Fv analogs, because of the avidity of the former (Id.). This characteristic of whole antibodies will provide stronger binding to antigen than single chain Fv analogs (Id.). As a result, diffusion of whole antibody therapeutics into tumors is prevented and, by remaining on the surface of solid tumors, such therapeutics will have the tendency to achieve better recruitment of immune effector cells from the blood (Id.). Since it is very hard to obtain any antibody with an affinity of >1 x 10^{-10} M, the diminished affinity of single chain Fv analogs will tend to impair their ability to bind to tumors avidly *in vivo* (Id.). The difference in avidity between whole antibodies and single chain Fv analogs is demonstrated by Adams et al., "High Affinity Restricts the Localization and Tumor Penetration of Single-Chain FV Antibody Molecules," Cancer Res, 61(12):4750-5 (2001) (Shin Declaration ¶ 6).

The half-life of whole antibodies is generally much longer than that of single chain Fv analogs (Shin Declaration ¶ 7). This prolonged half-life of antibodies increases bioavailability to tumors (Id.). Since single chain Fv analogs possess a short half-life, they must be frequently administered at a high dosage to achieve a desired anti-tumor efficacy (Id.). The difference in half-life between whole antibodies and single chain Fv analogs is demonstrated by Covell et al., "Pharmacokinetics of Monoclonal Immunoglobulin G1, F(ab')2, and Fab' in Mice," Cancer Res, 46(8):3969-78 (1986) and Goel et al., "^{99}mTc-Labeled Divalent and Tetravalent CC49 Single-Chain Fv's: Novel Imaging Agents for Rapid In Vivo Localization of Human Colon Carcinoma," J Nucl Med, 42(10):1519-27 (2001) (Shin Declaration ¶¶ 8-10).

Whole antibodies can carry two molecules of chemokines, but single chain Fv analogs carry only a single chemokine (Shin Declaration ¶ 11). Since chemokine receptors can form dimers, whole antibody fusion proteins carrying two chemokines would be much more effective cancer therapeutics than single chain Fv analog fusions (Id.). In addition, two chemokine molecules provide stronger binding to their receptors than single chain Fv

analogs, which would be dimerized after chemokine binding to transmit intracellular signals (Id.).

G-protein coupled receptors constitute a large family of homologous transmembrane proteins which are activated by a variety of different ligands such as chemokine, neurokinin, opioid, somatostatin, thyrotrophinm, and the whole biogenic amine family (Shin Declaration ¶ 11). G-protein coupled receptor can dimerize with the dimer being the functionally active form of the receptor (Id.).

Thus, an antibody carrying two chemokine molecules would tend to be more efficient at signaling through facilitation of receptor dimerization and/or crosslinking (Shin Declaration ¶ 12). This is demonstrated by Gouldson et al., "Lipid-Facing Correlated Mutations and Dimerization in G-Protein Coupled Receptors," Protein Eng, 14(10):759-767 (2001) and Vila-Coro et al., "The Chemokine SDF-1alpha Triggers CXCR4 Receptor Dimerization and Activates the JAK/STAT Pathway," FASEB J, 13(13):1699-710 (1999) (Shin Declaration ¶¶ 13-15).

Thus, it is apparent that one of ordinary skill in the art of antibody cancer therapeutics would not adapt teachings relating to single chain Fv analogs to cancer therapeutics relying on whole antibodies.

In response to the above points raised in the Shin Declaration, the examiner acknowledges that there are differences between single chain antibodies and conventional antibodies that have constant regions, but asserts that one would not have to adapt teachings relating to single chain antibodies as far as the characteristics discussed in the declaration to those on whole antibodies. This argument overlooks the points made in the Shin Declaration with regard to why single chain antibodies are so very different from conventional antibodies that one of ordinary skill in the art would not have considered teachings regarding the former to be useful with regard to the latter. In particular, the Shin Declaration demonstrates that scientists skilled in the field of antibody-based cancer therapeutics would have avoided adapting single chain Fv analog technology to whole antibody cancer therapeutics because of the fact that there are significant differences between single chain Fv analogs and whole antibodies with regard to the avidity, half life, and chemokine carriage. In other words, the requisite motivation to combine the references simply does not exist. See In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1458 (Fed. Cir. 1998) ("To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the

examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed."); Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1630 (Fed. Cir. 1996) ("It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references." (citation omitted)); See also In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). The examiner has provided no factual basis to support a contrary view by the Board. Accordingly, in view of the Shin Declaration, scientists skilled in the field of antibody-based cancer therapeutics would not regard information relating to immunoconjugates of single chain Fv analogs as relevant to immunoconjugates made from whole antibodies.

As a result of the absence of any motivation to combine Huston and Hölzer, the obviousness rejection of claims 1, 3-8, 10, and 25 based on the combination of these references is improper and should be withdrawn.

C. The Rejection of Claims 1 and 9 Under 35 U.S.C. § 103(a) for Obviousness Over Huston in View of Bacus and Hölzer Is Improper

1. Description of Huston

Huston is described in Section VIII(B)(2).

2. Description of Bacus

Bacus describes a method for determining the efficacy of a therapeutic agent, *in vitro*, for a cancer expressing or overexpressing an oncogene product. The method is particularly useful for determining the efficacy of therapeutic agents that have a binding affinity for cancer that express HER-2/neu. N24, N28, and N29 monoclonal antibodies are described which have been identified by this method. One or more of these antibodies can be used as a therapeutic agent in the treatment of breast, stomach, ovarian, or salivary cancers.

3. Description of Hölzer

Hölzer is described in Section VIII(B)(1).

4. The Combination of Huston, Bacus, and Hölzer Would Not Have Rendered the Claimed Invention Obvious

It is the examiner's position that the chimeric molecule comprising a chemokine coupled to the N-terminus of the heavy or light chain of a complete antibody, as disclosed in the present invention, would have been obvious in view of the combination of Huston, Bacus, and Hölzer. Huston is cited as teaching coupling the chemokine to the antibody by the N terminus. Bacus is cited as teaching monoclonal antibodies to her2/neu. Holzer is cited as teaching antibodies with chemokines attached at the C terminus.

Appellants submit that the combination of Huston, Bacus, and Hölzer do not establish a *prima facie* case of obviousness.

Hölzer does not satisfy the requirement of the claimed invention that the chemokine be "coupled to the N-terminus of the heavy or light chain of the antibody", since Hölzer's immunoconjugate binds the N-terminus of IL-8 to the carboxy terminus of the Fab fragment of the monoclonal antibody. In addition, the single-chain Fv analog of Huston lack the constant regions, C_H1, C_H2, and C_H3, unlike native IgG antibodies and, thus, is clearly distinguishable from the claimed complete antibody. Further, one of ordinary skill in the art would have no basis to adapt the teachings of Huston regarding single-chain Fv analogs to the whole antibody immunoconjugates of Hölzer, for all of the reasons set forth *supra*.

Since Bacus does not overcome the above-noted deficiencies of Huston and Hölzer, the obviousness rejection of claims 1 and 9 over Huston in view of Bacus and Hölzer is improper and should be withdrawn.

D. The Rejection of Claims 1, 3-10, and 25 Under 35 U.S.C. § 112 (2nd para.) for Indefiniteness Is Improper

The examiner has objected to the phrases "complete antibody" and "capable of binding" as recited in claim 1, stating that the exact meaning of the phrase is not clear. For the reasons noted below, the specification sufficiently defines the scope of these phrases such that one of ordinary skill in the art would understand their meaning.

1. The Phrase "complete antibody" Is Not Indefinite

One of ordinary skill in the art would readily understand that a complete antibody, like a whole antibody, contains all regions conventionally found in antibodies as opposed to fragments of antibodies. This is particularly true in view of the description in the specification of the structure of the claimed chimeric molecule and its "complete antibody" component.

The present application, at page 45, lines 14-16 and page 56, lines 28-32, describes chimeric molecules, RANTES.Her2.IgG3 and B7.her2.IgG3, having a complete or fully assembled H_2L_2 form (see also FIGS. 2, 3, and 10 showing chimeric molecules with a complete antibody structure). In addition, the term "antibodies" as used in the present application is defined at page 22, line 31 to page 23, line 4. The term refers to various types of immunoglobulin, including IgG, IgM, and IgA, and their relevant subclasses and also include antibody fragments such as, for example, Fab, $F(ab')_2$, and Fv fragments, and the corresponding fragments obtained from antibodies other than IgG (page 22, line 31 to page 23, line 4). Since the term "antibodies" in the present application is defined as including whole antibodies like IgG, IgM, and IgA, as well as antibody fragments, it is apparent that the phrase "complete antibody" means complete in the sense of having a complete structure, i.e. an antibody structure having V_H and V_L domains as well as constant regions C_H1, C_H2, and C_H3.

Further, it is well known by those skilled in the art that a complete antibody would mean a conventional antibody that not only contains V_H and V_L domains but also constant regions C_H1, C_H2, and C_H3. For example, Huston, which is one of the references cited by the examiner, shows a drawing of a complete antibody (i.e. IgG) containing V_H and V_L domains as well as constant regions C_H1, C_H2, and C_H3, with all of these components arranged with respect to one another in a particular fashion (page 49, Figure 1A).

Since those skilled in the art would fully understand what is meant by the phrase "complete antibody", the meaning of the phrase is not indefinite.

2. The Phrase "capable of binding" Is Not Indefinite

The objected phrase is recited in claim 1 which is directed to a chimeric molecule suitable for stimulating a tumor specific immune response comprising a complete antibody having heavy and light chains each with an N terminus and being capable of

specifically binding to a tumor cell associated antigen, and a chemokine, which is coupled to the N terminus of the heavy or light chain of the antibody such that the antibody remains capable of binding to the tumor cell associated antigen and the chemokine retains activity. One of ordinary skill in the art would fully understand antibody binding interactions and would not regard this phrase as indefinite. This is particularly true in view of the description in the specification of the binding capability of the antibody of the claimed chimeric molecule.

At page 17, lines 28-33, the present application describes how the antibody of the claimed chimeric molecule binds to a tumor cell associated antigen (see also page 21, lines 4-5 and page 45, line 26 to page 46, line 28). Thus, the chimeric molecule has a binding domain (which can be an antibody) which specifically binds to a tumor cell associated antigen from tumor cells which are breast cancer cells, ovarian cancer cells, lung cancer cells, prostate cancer cells, or other her2/neu expressing cancer cells (page 17, lines 28-33). In addition, the chimeric molecule preferably binds to a tumor cell associated antigen which is a cell surface antigen (page 21, lines 4-5). Further, Example 3, at page 45, line 26 to page 46, line 28, describes the testing of the ability of RANTES.Her2.IgG3 fusion protein to bind to the HER2/neu antigen. Both Her2.IgG3 (Figures 5b & e) and RANTES.Her2.IgG3 (Figures 5c & f) bound specifically to SKBR3 cells, a breast cancer cell line known to express high levels of HER2/neu (page 46, lines 1-3). Therefore, fusion of the extracellular domain of RANTES to the amino terminus of Her2.IgG3 did not interfere with recognition of the HER2/neu antigen by the antibody domain (page 46, lines 3-6). Since the binding capability of the antibody of the claimed chimeric molecule is thoroughly and adequately defined in the specification, one of ordinary skill in the art would fully comprehend the meaning of the phrase "capable of binding."

Moreover, as is apparent from the literal language of claim 1, what is being claimed is a chimeric molecule comprising a complete antibody and a chemokine. Thus, the antibody in the claimed chimeric molecule is not actually bound to a tumor cell associated antigen; the tumor cell associated antigen is only a potential target of the antibody. Since the claim is directed to a chimeric molecule comprising a complete antibody and a chemokine, one of ordinary skill in the art would fully comprehend that the antibody is not yet bound to a tumor cell associated antigen, but, as recited in the claim, is "capable of binding" to such an

antigen and is coupled to a chemokine such that it retains its capability to bind to such an antigen. Thus, the meaning of the phrase "capable of binding" is not indefinite.

Since the meaning of the claims is readily apparent to one of ordinary skill in the art, the rejection under 35 U.S.C. §112 (2^{nd} para.) should be withdrawn.

E. The Rejection of Claims 1, 3-10, and 25 Under 35 U.S.C. § 112 (1^{st} para.) for Lack of Descriptive Support Is Improper

It is the examiner's position that the specification does not provide descriptive support for the phrase "complete antibody" as recited in claim 1. For the reasons noted below, sufficient written descriptive support exists for the recited language.

At page 45, lines 14-16 and page 56, lines 28-32, the present application describes chimeric molecules, RANTES.Her2.IgG3 and B7.her2.IgG3, having a complete or fully assembled H_2L_2 form. In addition, FIGS. 2, 3, and 10 of the present application shows chimeric molecules with a complete antibody structure.

Moreover, it is well known by those skilled in the art that a complete antibody would mean a conventional antibody that not only contains V_H and V_L domains but also constant regions C_H1, C_H2, and C_H3. For example, Huston shows a drawing of an IgG antibody containing V_H and V_L domains as well as constant regions C_H1, C_H2, and C_H3, with all of these components arranged with respect to one another in a particular fashion (page 49, Figure 1A). In view of this knowledge by those skilled in the art and the fact that the present application clearly teaches the use of complete antibodies, one of ordinary skill in the art would fully understand that Appellants were in possession of the claimed invention.

Thus, the rejection under 35 U.S.C. § 112 (1^{st} para.) is improper and should be withdrawn.

IX. CONCLUSION

In view of the foregoing, it is clear that the rejections of the claims under 35 U.S.C. § 103(a), 35 U.S.C. § 112 (2nd para.), and 35 U.S.C. § 112 (1st para.) cannot be sustained. Accordingly, the rejections should be reversed.

Respectfully submitted,

Dated: November 4, 2003

Michael L. Goldman
Registration No. 30,727
Attorney for Appellants

Nixon Peabody LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1304
Facsimile: (585) 263-1600

Certificate of Mailing - 37 CFR 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450, on the date below.

Date	Ruth R. Smith
Nov. 4, 2003	Ruth R. Smith

APPENDIX

1. (previously presented) A chimeric molecule suitable for stimulating a tumor specific immune response comprising:

a complete antibody having heavy and light chains each with an N terminus and being capable of specifically binding to a tumor cell associated antigen, and

a chemokine, which is coupled to the N terminus of the heavy or light chain of the antibody such that the antibody remains capable of binding to the tumor cell associated antigen and the chemokine retains activity.

2. (canceled)

3. (previously presented) The chimeric molecule according to claim 1 wherein the chemokine is linked to the amino terminus of the light chain of the antibody.

4. (previously presented) The chimeric molecule according to claim 1, wherein the chemokine is linked to the amino terminus of the heavy chain of the antibody.

5. (previously presented) The chimeric molecule according to claim 1, further comprising:

a flexible linker or hinge region connecting the chemokine and the antibody.

6. (previously presented) The chimeric molecule according to claim 1, wherein the chemokine is selected from the group consisting of DC-CK1, SDF-1, fractalkine, lymphotactin, IP-10, Mig, MCAF, MIP-1α, MIP-1β, IL-8, NAP-2, PF-4, and RANTES.

7. (original) The chimeric molecule according to claim 6, wherein the chemokine is RANTES.

8. (previously presented) The chimeric molecule according to claim 1, wherein the antibody specifically binds to a tumor cell associated antigen from tumor cells selected from the group consisting of breast cancer cells, ovarian cancer cells, lung cancer cells, bladder cancer cells, and prostate cancer cells.

9. (previously presented) The chimeric molecule according to claim 1, wherein the antibody specifically binds to her2/neu.

10. (original) The chimeric molecule according to claim 1, wherein the tumor cell associated antigen is a cell surface antigen.

11-24 (canceled)

25. (original) A composition for stimulating a tumor specific immune response comprising:

the chimeric molecule according to claim 1, and
a pharmaceutically-acceptable carrier.

26-76 (canceled)